Rejection of claims 33-37 under 35 U.S.C. § 112, second paragraph

Claims 33-37 are rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness.

The Examiner states, "Claim 33 recites the limitation 'the activity'...[t]here is insufficient antecedent basis for this limitation in the claim."

Applicants submit that claim 33 has been amended to recite the "phosphorylation activity".

Applicants submit that the term "activity" is defined in the specification at p. 11, lines 15-16, wherein it is stated, "[t]he 'activity' of a signal transduction kinase is defined as the phosphorylation of target proteins." In view of the above, Applicants submit that the term "phosphorylation activity" refers to the phosphorylation activity of an RKIP-sensitive kinase, and is not indefinite.

The Examiner also asserts, that the metes and bounds for the phrases "an RKIP-sensitive kinase" and "the activity of an RKIP-sensitive kinase" are not clear.

Applicants submit that claim 33 has been amended to replace the phrase "RKIP-sensitive kinase" with the phrase "signal transduction kinase that binds an RKIP family member."

Applicants submits further that the term "signal transduction kinase" is defined in the specification at p. 11, lines 10-19, wherein it is stated,

> "The term "signal transduction kinase" refers to a kinase that is involved in one or more pathways involved in the transmission of signals originating outside the cell to the nucleus. Examples of signal transduction kinases include, but are not limited to Src, Raf-1 (GenBank Accession No. NM_002880), MEK, MEKK, MEKKK, ERK-1, ERK-2, NIK (GenBank Accession No. Y10256), TAK (GenBank Accession No. D76446), etc. of a cell for example, a kinase of the Raf/MEK/ERK or NF-κB signal transduction pathways. The "activity" of a signal transduction kinase is defined as the phosphorylation of target proteins. Alternatively, or in addition, "activity" of signal transduction proteins or the signal transduction pathway refers to the biological result of the phosphorylating activity of the kinase, including, for

example, cell proliferation, apoptosis, and cell transformation."

It is further stated in the specification at p. 7, lines 7-8, :[i]n one embodiment, the RKIP-sensitive kinase is selected from the group consisting of Raf, Mek, ERK, NIK and TAK."

Applicants submit that "binding" is defined in the instant application at p. 19, lines 7-20 as,

> "physical interaction between two molecules. The term refers to binding that is "specific", in that the binding molecule interacts with one or more target partners while excluding non-target molecules within a given sample. It is preferred, although not absolutely necessary, that binding result directly or indirectly in a change in a measurable characteristic of a sample. As used herein, binding is "inhibited" when a measure of the amount of a molecule bound decreases by at least 10%, and preferably by at least 20%, 50%, 75%, 80% 90%, 98% or more, up to and including 100% (no binding) relative to a chosen standard (e.g., a sample that does not contain a known or suspected inhibitor). Conversely, binding is "increased" or "enhanced" when a measure of the amount of a molecule bound increases by at least 10%, and preferably by at least 20%, 50%, 75%, 80% 90%, 98% or more, up to and including 100% or even more, including 2-fold, 5-fold, 10-fold or more relative to a chosen standard. Binding may be measured in a number of ways known to those of skill in the art, including but not limited to surface plasmon resonance, fluorescence polarization, FRET, scintillation proximity, pull-down assays, and yeast two-hybrid assays."

Applicants submit that the term "RKIP family" is defined on p. 12, lines 7-13, wherein it is stated, "[t]he term "RKIP family" means polypeptides or proteins that comprise an RKIP motif as defined herein.. all proteins belonging to the RKIP family have 1) a characteristic β fold structure formed by two anti-parallel β sheets, 2) a cavity capable of accepting an anion (preferably a phosphoryl moiety), and **3) the ability to specifically interact (or bind) with one or more signal transduction kinases**. A protein belonging to the RKIP family preferably includes the RKIP motif with the functional conserved amino acid residues indicated by arrows in Figure 1." (Emphasis added)

In view of all of the above, Applicants submit that the phrases "a signal transduction kinase that binds an RKIP family member" and "the activity of an RKIP-sensitive kinase" are both clearly defined in accordance with the requirements of 35 U.S.C. § 112, second paragraph.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejections of claims 33-37.

Rejection of claims 33-37 under 35 U.S.C. § 112, first paragraph

Claims 33-37 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to meet the written description requirement.

The Examiner asserts that claim 33 is drawn to a method of inhibiting a genus of kinases called "RKIP-sensitive kinase" using a "genus of agents". The Examiner states, "[b]ased on a species of so-called 'RKIP-sensitive kinase', i.e., Raf-1, and based on a species of agents, i.e., the human RKIP, one cannot predict additional species of 'RKIP-sensitive kinase' and additional species of agents other than the one shown in the instant specification. Since the genus include[s] a large number of unpredictable species, possession of a species from each of the two genuses is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicant adequately describe the method to inhibit activity of human Raf-1 kinase using the human RKIP protein shown in Fig. 8."

Applicants submit that the term "RKIP sensitive kinase" has been replaced with the phrase "a signal transduction kinase that binds an RKIP family member". Applicants submit that, as discussed above in Applicant's response to the 35 U.S.C. § 112, second paragraph rejection of claims 33-37, the terms "signal transduction kinase that binds an RKIP family member" and "RKIP family" are clearly defined. A list of signal transduction kinases, including their accession numbers is disclosed in the specification. Further, Example 1 teaches a method of identifying RKIP interacting proteins that could be used to determine if **any** candidate protein,

interacts with RKIP.

In view of the above, Applicants submit that the specification clearly teaches a plurality of "signal transduction kinases that bind an RKIP family member" in addition to Raf-1 kinase, as well as a method of detecting additional RKIP-sensitive kinases.

Claims 33-37 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.

The Examiner states that, [t]he specification teaches that the full-length RKIP inhibits Raf-1 kinase...but the specification does not teach any other agent that inhibits an RKIP-sensitive kinase[s]. The specification provides insufficient guidance with regard to what kinds of "agents" [are] able to inhibit an activity of an RKIP-sensitive kinase and provides no working examples which would provide guidance to one skilled in the art."

Applicants respectfully disagree.

Applicants submit that claim 33 has been amended to claim "an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif".

Applicants submit that "agent" is defined on p. 15, line 13- page 16, line 2, wherein it is stated,

> "[t]he term "agent" means a composition that has the capacity to modify the bioactivity of a nucleic acid encoding or polypeptide comprising an RKIP motif so as to modulate the activity of a signal transduction pathway that is responsive to an RKIP family protein. An "agent" as used herein may either promote or inhibit the function of the signal transduction pathway, the expression of genes regulated by that pathway, or the ultimate outcome of that pathway's activation (e.g., proliferation, apoptosis, differentiation, etc.). Agents can include any recombinant, modified or natural nucleic acid molecule, library of recombinant, modified or natural nucleic acid molecules, synthetic, modified or natural peptide, library of synthetic, modified or natural peptides; organic or inorganic compound, or library of organic or inorganic compounds

> (including small molecules) where the agent has the capacity to modify the bioactivity of an RKIP motif-bearing polypeptide."

The specification also includes a comprehensive section entitled, "Candidate Agents" at p. 60-66 that teaches candidate agents and properties thereof, useful according to the invention.

The term "RKIP motif" is defined on p. 8, line 20- p. 9, line 9 as,

> "A motif on a polypeptide characterized by the consensus amino acid sequence $TLX_3DPD(Z)PX_3(B)X_4EX_2H\ X_nYX_4PX_{(2-4)}GXHR(O)VX(Z)X_3Q$ wherein the single letter amino acid code is in accordance with the IUB/IUPAC code, X may be any amino acid, Z indicates a hydrophobic amino acid residue, B indicates negatively charged amino acid residue (D or E), O indicates an aromatic amino acid residue (Y or F), and n is an integer from about 10 to about 50. A sequence does not have to be a perfect match with the consensus in order to be an RKIP motif, but must be comprised within a β fold structure composed of two antiparallel β sheets within the molecule. A sequence that is an RKIP motif is at preferably at least about 70% similar to the consensus sequence, more preferably about 75% similar, 80% similar, 85% similar, 90% similar, 95% similar, 98% similar or even 100% similar or most preferably, identical to the consensus. Further, the RKIP sequence motif and polypeptides comprising it interact specifically with one or more signal transduction kinases."

Applicants also submit that the term "activity" is defined at p. 16, line 7-22 as

> "An effector or antigenic function that is directly or indirectly performed by a polypeptide (whether in its native or denatured conformation), or by any subsequence thereof. Bioactivities include binding to polypeptides, binding to other proteins or molecules, activity as a DNA binding protein, as a transcription regulator, ability to bind damaged DNA, etc. A bioactivity can be modulated by directly affecting the subject polypeptide. Alternatively, a bioactivity can be altered by modulating the level of the polypeptide, such as by modulating expression of the corresponding gene. The activity of an RKIP motif-containing polypeptide is increased by a modulating agent if an effector function of such polypeptide, as measured by any of the assay methods described herein (e.g., partner binding assays,

> transcription assays, transformation assays, kinase assays, etc.), is increased by at least 10%, and preferably at least 20%, 35%, 50%, 75%, 100%, or even 2-fold, 5-fold, 10-fold, 50-fold or more relative to a sample in which no agent was present. The activity of an RKIP motif-containing polypeptide is decreased by a modulating agent if an effector function of such polypeptide, as measured by any of the assay methods described herein, is reduced by at least 10%, and preferably at least 20%, 35%, 50%, 75%, 90%, 95%, or even up to and including 100% (i.e., no activity)."

Applicants also submit that the term "increase" is defined on p. 17, lines 1-7 as "a function of an 'agonist' which is meant to refer to an agent that mimics or upregulates (e.g., potentiates or supplements) the bioactivity of a protein. An agonist can be a wild-type protein or derivative thereof having at least one bioactivity of the wild-type protein. An agonist can also be a compound that upregulates expression of a gene or which increases at least one bioactivity of a protein. An agonist can also be a compound which increases the interaction of a polypeptide with another molecule, e.g., a target peptide or nucleic acid."

Applicants submit further that the term "inhibit" is defined on p. 18, lines 6-12, as a function by an 'antagonist' which refers to an agent that downregulates (e.g., suppresses or inhibits) at least one bioactivity of a protein. An antagonist can be a compound which inhibits or decreases the interaction between a protein and another molecule, e.g., a target peptide or enzyme substrate. An antagonist can also be a compound that downregulates expression of a gene or which reduces the amount of expressed protein present. An antagonist [inhibits] bioactivity if it reduces that activity by at least 10%, preferably by at least 20%, 30%, 50%, 75%, 95%, 98%, and up to and including 100%."

Applicants submit further that the term "RKIP family" is defined in the specification at p. 12, lines 7-13, as polypeptides or proteins that comprise an RKIP motif as defined herein... all proteins belonging to the RKIP family have 1) a characteristic β fold structure formed by two anti-parallel β sheets, 2) a cavity capable of accepting an anion (preferably a phosphoryl moiety), and **3) the ability to specifically interact (or bind) with one or more signal transduction**

**kinases**. A protein belonging to the RKIP family preferably includes the RKIP motif with the functional conserved amino acid residues indicated by arrows in Figure 1." (Emphasis added)

It is also stated at p.58, line 20- p. 59, line 1, "[b]ecause RKIP family members inhibit kinase activity, monitoring the activity of these target kinases in the presence or absence of candidate RKIP modulators permits one to determine the effect of a candidate modulator on RKIP activity."

In view of the above, Applicants submit that the term "agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif" clearly encompasses, but is not limited to RKIP. That is, as disclosed in the specification, an "agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif" includes RKIP, as well as compositions that "modify the bioactivity of a nucleic acid encoding or polypeptide comprising an RKIP motif so as to modulate the activity of a signal transduction pathway that is responsive to an RKIP family protein."

The Examiner has also rejected claim 35 for alleged lack of enablement. The Examiner states that claim 35 is "drawn to a method of inhibiting [an] 'RKIP-sensitive kinase' comprising contacting said kinase with a polypeptide comprising an RKIP motif." The Examiner has interpreted this claim as being drawn to a method of regulating cell proliferation or apoptosis, comprising the active step of contacting a cell expressing RKIP-sensitive kinase with a polypeptide comprising an RKIP motif. The Examiner also states that the specification does not teach how to regulate apoptosis or proliferation of a cell by contacting the RKIP.

Applicants respectfully disagree.

Applicants submit that claim 35 should not be interpreted as being drawn only to modulation of cell proliferation and differentiation. It is stated in the specification at p. 15, lines 15-18, [a]n agent as used herein may either promote or inhibit the function of the signal transduction pathway, the expression of genes regulated by that pathway, or the **ultimate**

**outcome of that pathway's activation (e.g., proliferation, apoptosis, differentiation** etc...). (Emphasis added) It is also stated at p. 58, line 19-p. 59, line 3, [t]he phosphorylation of kinase targets may be monitored as a more direct assay for RKIP activity." In view of the above, Applicants submit that claim 35 encompasses modulation of the activity of an RKIP-sensitive kinase, as defined in the instant application (p. 11, lines 15-16, wherein it is stated, "[t]he 'activity' of a signal transduction kinase is defined has the phosphorylation of target proteins."). One of skill in the art would accept that changes in apoptosis and proliferation resulting from modulation of the activity of a kinase are due to changes in kinase activity. The specification teaches how to measure the modulation of the phosphorylation activity of an RKIP-sensitive kinase in Example 5, entitled, "Inhibition of Raf-1 phosphorylation of MEK by RKIP" and Example 6, entitled, "In vivo regulation of MEK and ERK activation by RKIP".

In view of the above, Applicants submits that claim 35 is clearly enabled in accordance with the legal requirements of 35 U.S.C. § 112, first paragraph.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 112, first paragraph rejections of claim 33-37.

Rejection of claims 33, 34, 36 and 37 Under 35 U.S.C. § 102

Claims 33, 34, 36 and 37 are rejected under 35 U.S.C. § 102(b) for alleged lack of novelty in view of Jelinek et al. (March 1996, Molecular and Cellular Biology, Vol. 16, pp. 1027-1034).

The Examiner states, [t]he claims are drawn to a method of inhibiting the activity of RKIP-sensitive kinase, comprising contacting said kinase with an agent, wherein the agent is a polypeptide in claim 34, wherein the kinase is a MAPK/ERK kinase in claim 36, wherein the agent binds to Raf-1 in claim 37. Jelinek et al. teach...a method of inhibiting Raf-1 by PTP-1B.

Applicants submit that Jelinek et al. teach inactivation of Ras by the protein tyrosine

phosphatase PTB-1B. Jelinek et al. do not teach that PTB-1B is an "agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif", as recited in claim 33 and as defined in the instant application.

Claim 33 claims "a method of inhibiting the phosphorylation activity of a signal transduction kinase that binds an RKIP family member, comprising the step of contacting said signal transduction kinase with an amount of an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif, wherein said agent inhibits the phosphorylation activity of said signal transduction kinase that binds an RKIP family member."

Claim 34 adds the limitation, wherein said agent is a polypeptide.

Claim 36 adds the limitation wherein said kinase is a MAPK/ERK kinase.

Claim 37 adds the limitation wherein said agent binds to Raf-1.

Applicants submit that "agent" is defined on p. 15, line 13- page 16, line 2, wherein it is stated,

> "[t]he term "agent" means **a composition that has the capacity to modify the bioactivity of a nucleic acid encoding or polypeptide comprising an RKIP motif so as to modulate the activity of a signal transduction pathway that is responsive to an RKIP family protein**. An "agent" as used herein may either promote or inhibit the function of the signal transduction pathway, the expression of genes regulated by that pathway, or the ultimate outcome of that pathway's activation (e.g., proliferation, apoptosis, differentiation, etc.). Agents can include any recombinant, modified or natural nucleic acid molecule, library of recombinant, modified or natural nucleic acid molecules, synthetic, modified or natural peptide, library of synthetic, modified or natural peptides; organic or inorganic compound, or library of organic or inorganic compounds (including small molecules) where the agent has the capacity to modify the bioactivity of an RKIP motif-bearing polypeptide." (Emphasis added)

Applicants submit that Jelinek et al. do not teach that PTP-1B is **a composition that**

**increases or inhibits the activity of a polypeptide comprising an RKIP motif so as to modulate the activity of a signal transduction pathway that is responsive to an RKIP family protein**, and therefore do not anticipate any of claims 33, 34, 36 or 37. Applicants submit further that Jelinek et al. do not teach a method of inhibiting the phosphorylation activity of a signal transduction kinase that binds an RKIP family member, comprising the step of contacting said signal transduction kinase with an amount of an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif, wherein said agent inhibits the phosphorylation activity of said signal transduction kinase that binds an RKIP family member, as claimed in claim 33 and dependent claims 34, 36 and 37, and therefore do not anticipate any of claims 33, 34, 36 and 37.

Claims 33 and 36 are rejected under 35 U.S.C. § 102(e) for alleged lack of novelty in view of U.S. 6,187,799.

The Examiner states, "[t]he claims are drawn to a method of inhibiting the activity of RKIP-sensitive kinase, comprising contacting said kinase with an agent, wherein the kinase is a MAPK/ERK kinase in claim 36. U.S. Patent 6,187,799...teaches a method of inhibiting Raf kinase with several different agents."

Applicants respectfully disagree.

Applicants submit that U.S. 6,187,799 teach methods of treating tumors mediated by raf kinase using substituted urea compounds.

Applicants also submit that U.S. 6,187,799 do not teach that any of the disclosed urea compounds are an "agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif", as defined in the instant application.

Claim 33 claims "a method of inhibiting the phosphorylation activity of a signal transduction kinase that binds an RKIP family member, comprising the step of contacting said signal transduction kinase with an amount of an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif, wherein said agent inhibits the phosphorylation activity

of said signal transduction kinase that binds an RKIP family member."

Claim 34 adds the limitation, wherein said agent is a polypeptide.

Claim 36 adds the limitation wherein said kinase is a MAPK/ERK kinase.

Applicants submit that U.S. 6,187,799 do not teach an agent that as defined in the instant application that is **a composition that increases or inhibits the activity of a polypeptide comprising an RKIP motif so as to modulate the activity of a signal transduction pathway that is responsive to an RKIP family protein**. Applicants submit further that U.S. 6,187,799 do not teach a method of inhibiting the phosphorylation activity of a signal transduction kinase that binds an RKIP family member, comprising the step of contacting said signal transduction kinase with an amount of an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif, wherein said agent inhibits the phosphorylation activity of said signal transduction kinase that binds an RKIP family member, as claimed in claim 33 and dependent claims 34 and 36 and therefore do not anticipate any of claims 33, 34 or 36.

In view of all of the above, Applicants respectfully request withdrawal of the 35 U.S.C. § 102 rejection of claims 33, 34, 36 and 37.

Applicant submits that, in view of the above, the claims are patentable and are in condition for allowance. A notice of allowance to that effect is respectfully requested.

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Date

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MARKED UP CLAIMS

33. (Amended) A method of inhibiting the phosphorylation activity of [an RKIP-sensitive kinase] a signal transduction kinase that binds an RKIP family member, comprising the step of contacting said RKIP-sensitive kinase with an amount of an agent that increases or inhibits the activity of a polypeptide comprising an RKIP motif, wherein said agent [which] inhibits the activity of said [RKIP-sensitive kinse] signal transduction kinase that binds an RKIP family member, sufficient to inhibit said activity.